

ANTI-TAU ANTIBODIES AND METHODS OF USE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority of US Provisional Application No. 62/171,693, filed June 5, 2015, which is incorporated by reference herein in its entirety for any purpose.

FIELD OF THE INVENTION

[0002] The present invention relates to anti-Tau antibodies and methods of using the same.

BACKGROUND

[0003] Neurofibrillary tangles and neuropil threads (NTs) are the major neuropathological hallmarks of Alzheimer's Disease (AD). NTs are composed of the microtubule-associated Tau protein that has undergone post-translational modifications including phosphorylation, and develop by aggregation of hyperphosphorylated Tau conformers. AD shares this pathology with many neurodegenerative tauopathies, in particular with certain types of frontotemporal dementia (FTD). Tau protein appears to be a major player in the cognitive demise in AD and related neurodegenerative tauopathies.

[0004] Therapeutic approaches that target Tau protein are scarce and comprise mainly inhibitors of the kinases that are thought to increase the phosphorylation of Tau to pathological levels, and compounds that block the cytoplasmic aggregation of hyper-phosphorylated Tau protein. These approaches suffer various draw-backs of specificity and efficacy. There is a need for additional therapeutic agents that target the pathological protein conformers that are known or presumed to cause neurodegenerative disorders.

SUMMARY

[0005] The disclosure provides anti-Tau antibodies and methods of using the same.

[0006] In one aspect, an isolated antibody that binds to human Tau is provided, wherein the antibody binds to monomeric Tau, oligomeric Tau, non-phosphorylated Tau, and phosphorylated Tau. In some embodiments, the antibody binds an epitope within amino acids 2 to 24 of mature human Tau. In some embodiments, the antibody is a monoclonal antibody. In some embodiments, the antibody is a human, humanized, or chimeric

- q) a light chain variable region (VL) comprising the sequence of SEQ ID NO: 31;
- r) a VH as in (p) and a VL as in (q);
- s) a heavy chain variable region (VH) comprising the sequence of SEQ ID NO: 50;
- t) a light chain variable region (VL) comprising the sequence of SEQ ID NO: 51; or
- u) a VH as in (s) and a VL as in (t).

[0012] In some embodiments, the antibody comprises HVR-H1 comprising the amino acid sequence of SEQ ID NO: 342; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 343; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 344; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 345; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 346; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 347.

[0013] In some embodiments, the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 340 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 341.

[0014] In some embodiments, the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 348 or SEQ ID NO: 602 and a light chain comprising the amino acid sequence of SEQ ID NO: 349.

[0015] In one aspect, an isolated antibody that binds to human Tau is provided, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 348 or SEQ ID NO: 602 and a light chain comprising the amino acid sequence of SEQ ID NO: 349. In some embodiments, an isolated antibody that binds to human Tau is provided, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 348 and a light chain comprising the amino acid sequence of SEQ ID NO: 349. In some embodiments, an isolated antibody that binds to human Tau is provided, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 602 and a light chain comprising the amino acid sequence of SEQ ID NO: 349. In one aspect, an isolated antibody that binds to human Tau is provided, wherein the antibody comprises a heavy chain consisting of the amino acid sequence of SEQ ID NO: 348 or SEQ ID NO: 602 and a light chain consisting of the amino acid sequence of SEQ ID NO: 349. In some embodiments, an isolated antibody that binds to human Tau is provided, wherein the antibody comprises a heavy chain consisting of the amino acid sequence of SEQ ID NO: 348 and a light

- bbb) a VH as in (zz) and a VL as in (aaa);
- ccc) a heavy chain variable region (VH) comprising the sequence of
SEQ ID NO: 260;
- ddd) a light chain variable region (VL) comprising the sequence of
SEQ ID NO: 261; or
- eee) a VH as in (ccc) and a VL as in (ddd).

[0022] In any of the embodiments described herein, the antibody may be an IgG1 or an IgG4 antibody. In any of the embodiments described herein, the antibody may be an IgG4 antibody. In some such embodiments, the antibody comprises M252Y, S254T, and T256E mutations. In any of the embodiments described herein, the antibody may comprise an S228P mutation. In any of the embodiments described herein, the antibody may comprise S228P, M252Y, S254T, and T256E mutations. In any of the embodiments described herein, the antibody may be an IgG4 antibody comprising S228P, M252Y, S254T, and T256E mutations. In some embodiments, the antibody is an antibody fragment. In any of the embodiments described herein, the antibody may be an IgG4 antibody comprising S228P, M252Y, S254T, and T256E mutations, and lacking the C-terminal lysine (des-K) of the heavy chain constant region. The C-terminal lysine of the heavy chain constant region may be removed, for example, during purification of the antibody or by recombinant engineering of the nucleic acid encoding the antibody such that the C-terminal lysine is not encoded.

[0023] In some embodiments, an isolated antibody that binds human Tau is provided, wherein the antibody binds each of monomeric Tau, phosphorylated Tau, non-phosphorylated Tau, and oligomeric Tau with a K_D of less than 100 nM, less than 75 nM, or less than 50 nM. In some embodiments, the antibody binds cynomolgus monkey Tau (SEQ ID NO: 4).

[0024] In one aspect, an isolated nucleic acid is provided, wherein the isolated nucleic acid encodes an antibody described herein. In one aspect, a host cell is provided, wherein the host cell comprises an isolated nucleic acid that encodes an antibody described herein. In one aspect, a method of producing an antibody is provided, comprising culturing the host cell described herein under conditions suitable for producing the antibody.

[0025] In one aspect, an immunoconjugate is provided, wherein the immunoconjugate comprises an isolated antibody described herein and a second therapeutic agent. In one aspect, a labeled antibody is provided, comprising an antibody described herein and a detectable label.

[0026] In one aspect, a pharmaceutical composition is provided, comprising an isolated antibody described herein and a pharmaceutically acceptable carrier.

[0027] In some embodiments, a method of treating a Tau protein associated disease is provided, comprising administering to an individual with a Tau protein related disease an antibody described herein or a pharmaceutical composition comprising an antibody described herein. In some embodiments, the Tau protein associated disease is a tauopathy. In some embodiments, the tauopathy is a neurodegenerative tauopathy. In some embodiments, the tauopathy is selected from Alzheimer's Disease, amyotrophic lateral sclerosis, Parkinson's disease, Creutzfeldt-Jacob disease, Dementia pugilistica, Down's Syndrome, Gerstmann-Sträussler-Scheinker disease, inclusion-body myositis, prion protein cerebral amyloid angiopathy, traumatic brain injury, amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam, Non-Guamanian motor neuron disease with neurofibrillary tangles, argyrophilic grain dementia, corticobasal degeneration, diffuse neurofibrillary tangles with calcification, frontotemporal dementia, frontotemporal dementia with parkinsonism linked to chromosome 17, Hallevorden-Spatz disease, multiple system atrophy, Niemann-Pick disease type C, Pallido-ponto-nigral degeneration, Pick's disease, progressive subcortical gliosis, progressive supranuclear palsy, Subacute sclerosing panencephalitis, Tangle only dementia, Postencephalitic Parkinsonism, and Myotonic dystrophy. In some embodiments, the tauopathy is Alzheimer's disease or progressive supranuclear palsy.

[0028] In some embodiments, a method of retaining or increasing cognitive memory capacity or slowing memory loss in an individual is provided, comprising administering an antibody described herein or a pharmaceutical composition comprising an antibody described herein.

[0029] In some embodiments, a method of reducing the level of Tau protein, non-phosphorylated Tau protein, phosphorylated Tau protein, or hyperphosphorylated Tau protein in an individual is provided, comprising administering an antibody described herein or a pharmaceutical composition comprising an antibody described herein.

[0030] In one aspect, an isolated antibody described herein is provided for use as a medicament. In one aspect, an isolated antibody described herein is provided for use in treating a tauopathy in an individual. In some embodiments, the tauopathy is a neurodegenerative tauopathy. In some embodiments, the tauopathy is selected from Alzheimer's Disease, amyotrophic lateral sclerosis, Parkinson's disease, Creutzfeldt-Jacob disease, Dementia pugilistica, Down's Syndrome, Gerstmann-Sträussler-Scheinker disease, inclusion-body myositis, prion protein cerebral amyloid angiopathy, traumatic brain injury, amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam, Non-Guamanian motor neuron disease with neurofibrillary tangles, argyrophilic grain dementia, corticobasal

degeneration, diffuse neurofibrillary tangles with calcification, frontotemporal dementia, frontotemporal dementia with parkinsonism linked to chromosome 17, Hallevorden-Spatz disease, multiple system atrophy, Niemann-Pick disease type C, Pallido-ponto-nigral degeneration, Pick's disease, progressive subcortical gliosis, progressive supranuclear palsy, Subacute sclerosing panencephalitis, Tangle only dementia, Postencephalitic Parkinsonism, and Myotonic dystrophy. In some embodiments, the tauopathy is Alzheimer's disease or progressive supranuclear palsy.

[0031] In one aspect, an isolated antibody described herein is provided for use in retaining or increasing cognitive memory capacity or slowing memory loss in an individual. In one aspect, an isolated antibody described herein is provided for use in reducing the level of Tau protein, phosphorylated Tau protein, non-phosphorylated Tau protein, or hyperphosphorylated Tau protein in an individual.

[0032] In one aspect, use of an antibody or pharmaceutical composition described herein is provided in the manufacture of a medicament for treating a Tau protein associated disease in an individual. In some embodiments, the Tau protein associated disease is a tauopathy. In some embodiments, the tauopathy is a neurodegenerative tauopathy. In some embodiments, the tauopathy is selected from Alzheimer's Disease, amyotrophic lateral sclerosis, Parkinson's disease, Creutzfeldt-Jacob disease, Dementia pugilistica, Down's Syndrome, Gerstmann-Sträussler-Scheinker disease, inclusion-body myositis, prion protein cerebral amyloid angiopathy, traumatic brain injury, amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam, Non-Guamanian motor neuron disease with neurofibrillary tangles, argyrophilic grain dementia, corticobasal degeneration, diffuse neurofibrillary tangles with calcification, frontotemporal dementia, frontotemporal dementia with parkinsonism linked to chromosome 17, Hallevorden-Spatz disease, multiple system atrophy, Niemann-Pick disease type C, Pallido-ponto-nigral degeneration, Pick's disease, progressive subcortical gliosis, progressive supranuclear palsy, Subacute sclerosing panencephalitis, Tangle only dementia, Postencephalitic Parkinsonism, and Myotonic dystrophy. In some embodiments, the tauopathy is Alzheimer's disease or progressive supranuclear palsy.

[0033] In one aspect, use of an antibody or pharmaceutical composition described herein is provided in the manufacture of a medicament for retaining or increasing cognitive memory capacity or slowing memory loss in an individual.

[0033a] In one aspect, use of an antibody or pharmaceutical composition described herein is provided in the manufacture of a medicament for reducing the level of Tau protein, non-phosphorylated Tau protein, phosphorylated Tau protein, or hyperphosphorylated Tau protein in an individual.

[0034] In one aspect, a method of detecting neurofibrillary tangles, neuropil threads, or dystrophic neuritis is provided, comprising contacting a sample with an antibody

32. A method of producing an antibody comprising culturing the host cell of claim 31 under conditions suitable for producing the antibody.

33. An immunoconjugate comprising the isolated antibody of any one of claims 1 to 29 and a second therapeutic agent.

34. A labeled antibody comprising the antibody of any one of claims 1 to 28 and a detectable label.

35. A pharmaceutical composition comprising the isolated antibody of any one of claims 1 to 29 and a pharmaceutically acceptable carrier.

36. Use of the antibody of any one of claims 1 to 29 or the pharmaceutical composition of claim 33 in the manufacture of a medicament for treating a Tau protein associated disease in an individual.

37. The use of claim 36, wherein the Tau protein associated disease is a tauopathy.

38. The use of claim 37, wherein the tauopathy is a neurodegenerative tauopathy.

39. The use of claim 37 or claim 38, wherein the tauopathy is selected from Alzheimer's Disease, amyotrophic lateral sclerosis, Parkinson's disease, Creutzfeldt-Jacob disease, Dementia pugilistica, Down's Syndrome, Gerstmann-Sträussler-Scheinker disease, inclusion-body myositis, prion protein cerebral amyloid angiopathy, traumatic brain injury, amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam, Non-Guamanian motor neuron disease with neurofibrillary tangles, argyrophilic grain dementia, corticobasal degeneration, diffuse neurofibrillary tangles with calcification, frontotemporal dementia, frontotemporal dementia with parkinsonism linked to chromosome 17, Hallevorden-Spatz disease, multiple system atrophy, Niemann-Pick disease type C, Pallido-ponto-nigral degeneration, Pick's disease, progressive subcortical gliosis, progressive supranuclear palsy, Subacute sclerosing panencephalitis, Tangle only dementia, Postencephalitic Parkinsonism, and Myotonic dystrophy.

40. The use of any one of claims 37 to 39, wherein the tauopathy is Alzheimer's disease or progressive supranuclear palsy.

41. Use of the antibody of any one of claims 1 to 29 or the pharmaceutical composition of claim 35 in the manufacture of a medicament for retaining or increasing cognitive memory capacity or slowing memory loss in an individual.

42. Use of the antibody of any one of claims 1 to 29 or the pharmaceutical composition of claim 35 in the manufacture of a medicament for reducing the level of Tau protein, non-phosphorylated Tau protein, phosphorylated Tau protein, or hyperphosphorylated Tau protein in an individual.

43. The use of any one of claims 36 to 42, wherein the medicament is to be administered with at least one additional therapy.

44. The use of claim 43, wherein the additional therapy is selected from neurological drugs, corticosteroids, antibiotics, antiviral agents, anti-Tau antibodies, Tau inhibitors, anti-amyloid beta antibodies, beta-amyloid aggregation inhibitors, anti-BACE1 antibodies, and BACE1 inhibitors.

45. The isolated antibody of any one of claims 1 to 29 for use as a medicament.

46. The isolated antibody of any one of claims 1 to 29 for use in treating a tauopathy in an individual.

47. The isolated antibody of claim 46, wherein the tauopathy is a neurodegenerative tauopathy.

48. The isolated antibody of claim 46 or claim 47, wherein the tauopathy is selected from Alzheimer's Disease, amyotrophic lateral sclerosis, Parkinson's disease, Creutzfeldt-Jacob disease, Dementia pugilistica, Down's Syndrome, Gerstmann-Sträussler-Scheinker disease, inclusion-body myositis, prion protein cerebral amyloid angiopathy, traumatic brain injury, amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam, Non-Guamanian motor neuron disease with neurofibrillary tangles, argyrophilic grain dementia, corticobasal degeneration, diffuse neurofibrillary tangles with calcification, frontotemporal dementia, frontotemporal dementia with parkinsonism linked to chromosome 17, Hallevorden-Spatz disease, multiple system atrophy, Niemann-Pick disease type C, Pallido-ponto-nigral degeneration, Pick's disease, progressive subcortical gliosis, progressive supranuclear palsy, Subacute sclerosing panencephalitis, Tangle only dementia, Postencephalitic Parkinsonism, and Myotonic dystrophy.

49. The isolated antibody of any one of claims 46 to 48, wherein the tauopathy is Alzheimer's disease or progressive supranuclear palsy.

50. An isolated antibody of any one of claims 1 to 29 for use in retaining or increasing cognitive memory capacity or slowing memory loss in an individual.

51. An isolated antibody of any one of claims 1 to 29 for use in reducing the level of Tau protein, phosphorylated Tau protein, non-phosphorylated Tau protein, or hyperphosphorylated Tau protein in an individual.

52. The isolated antibody of any one of claims 46 to 51, wherein the antibody is for use with at least one additional therapy.

53. The isolated antibody of claim 52, wherein the additional therapy is selected from neurological drugs, corticosteroids, antibiotics, antiviral agents, anti-Tau antibodies, anti-amyloid beta antibodies, anti-BACE1 antibodies, and BACE1 inhibitors.

54. A method of detecting neurofibrillary tangles, neurophil threads, or dystrophic neuritis comprising contacting a sample with the antibody of any one of claims 1 to 29.

55. The method of claim 54, wherein the sample is a brain sample, a cerebrospinal fluid sample, or a blood sample.